REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 71-78 and 86-105 are pending in the application subsequent to entry of this Amendment.

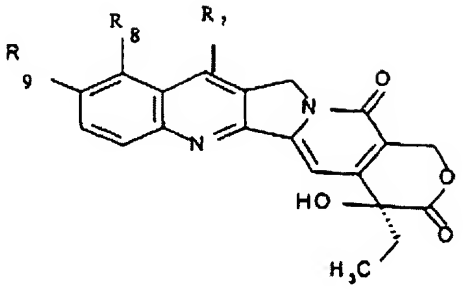
Amendment of the Claims/Response to Claim Clarity Rejection

In item 2 of the Official Action claims 79-93 were criticized as being indefinite. Claims 79-85 have been withdrawn in light of the examiner's comment and claim 86 is amended to delete mention of substances with cosmetic activity. Thus the issues raised in item 2 of the Official Action are resolved by amendment of the claims. In addition, claims 79-85 and 106 have been withdrawn in order to reduce issues. This action is taken without disclaimer and without prejudice to continuing applications directed to the subject matter of these claims.

Response to Claim Rejections – 35 USC §103(a)

The official Action includes two separate rejections. The first in item 4 cites Wang with Allen, Burke and Stracher against claims 71-105; the second in item 5 cites Hsu in combination with Wang against a slightly different grouping of claims, claims 76-106. Applicants traverse both rejections – the prior art cited and combined in a manner such as set out in the Action is not suggestive of the subject matter of applicants' claims.

To establish a case of *prima facie* obviousness, all of the claim limitations must be taught or suggested by the prior art. *See* M.P.E.P. § 2143.03. A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing the legal standard provided in *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. *See id.* ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. *See id.* at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a *prima facie* case of obviousness



wherein: R_7 is a $-C(R_{11})=N-O_{(n)}R_{10}$ group, wherein R_{10} is hydrogen or a C_1-C_5 alkyl or C_2-C_5 alkenyl group, linear or branched or C_3-C_{10} cycloalkyl, group or a linear or branched (C_3-C_{10}) cycloalkyl - (C_1-C_5) alkyl group, or C_6-C_{14} aryl, or a linear or branched (C_6-C_{14}) aryl - (C_1-C_5) alkyl group, or a heterocyclic or linear or branched heterocyclo - (C_1-C_5) alkyl group, said heterocyclic group containing at least a heteroatom selected from the group consisting of nitrogen atom, optionally substituted with a (C_1-C_5) alkyl group, and/or oxygen and/or sulfur; said alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aryl-alkyl, heterocyclic or heterocyclo-alkyl groups, being optionally substituted with other groups selected from the group consisting of: halogen, hydroxy, C_1-C_5 alkyl, C_1-C_5 alkoxy, phenyl, cyano, nitro, $-NR_{12}R_{13}$, wherein R_{12} and R_{13}, which may be the same or different, are hydrogen, linear or branched (C_1-C_5) alkyl; a pharmaceutically acceptable ester of the –COOH group; or the–$CONR_{14}R_{15}$ group, wherein R_{14} and R_{15}, which may be the same or different, are hydrogen or linear or branched (C_1-C_5) alkyl; or

R_{10} is a (C_6-C_{10}) aroyl residue optionally substituted by one or more groups selected from the group consisting of: halogen, hydroxy, linear or branched (C_1-C_5) alkyl, C_1-C_5 alkoxy, phenyl, cyano, nitro, $-NR_{16}R_{17}$, wherein R_{16} and R_{17}, which may be the same or different, are hydrogen, linear or branched (C_1-C_8) alkyl;

n is the number 0 or 1;

R_{11} is hydrogen, linear or branched C_1-C_5 alkyl, linear or branched C_2-C_5 alkenyl, C_3-C_{10} cycloalkyl, (C_3-C_{10}) cycloalkyl - linear or branched (C_1-C_5) alkyl, C_6-C_{14} aryl, (C_6-C_{14}) aryl - linear or branched alkyl (C_1-C_5);

R_8 and R_9, which may be the same or different is hydrogen, hydroxy, linear or branched C_1-C_5 alkoxy;

their N_1-oxides, their single isomers, in particular the syn and anti isomers of the– $C(R_{11})$=N-$O_{(n)}R_{10}$ group, their possible enantiomers, diastereoisomers and relative admixtures, the pharmaceutically acceptable salts thereof~~; or~~

~~said liposome comprising a substance with cosmetic activity~~.

87. (Previously Presented) The composition according to claim 86, in which R_3 is selected from the group consisting of nonanoyl, dodecanoyl, myristoyl, palmitoyl, stearoyl and oleolyl.

88. (Previously Presented) The composition according to claim 86, in which R_4 is selected from the group consisting of nonyl, undecyl, tetradecyl, hexadecyl and oleyl.

89. (Previously Presented) The composition according to claim 86, in which X– is selected from the group consisting of chloride; bromide; iodide; aspartate; acid aspartate; citrate; acid citrate; tartrate; acid tartrate; phosphate; acid phosphate; fumarate; acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate; acid maleate; mucate; orotate; oxalate; acid oxalate; sulphate; acid sulphate; trichloroacetate; trifluoroacetate; methane sulphonate; pamoate and acid pamoate.

90. (Previously Presented) The composition according to claim 86, in which the compound is selected from the group consisting of: palmitoyl L-carnitine chloride undecyl ester; stearoyl L-carnitine chloride undecyl ester; stearoyl L-carnitine chloride tetradecyl ester;

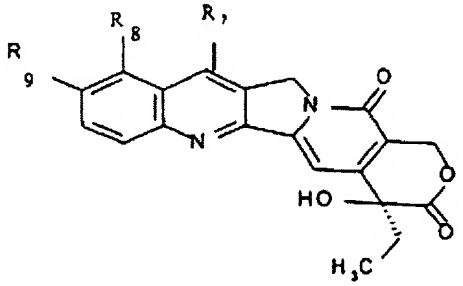
palmitoyl L-carnitine chloride tetradecyl ester; myristoyl L-carnitine chloride tetradecyl ester; palmitoyl L-carnitine bromide hexadecyl ester, and oleolyl L-carnitine chloride oleyl ester.

91. (Previously Presented) The composition according to according to claim 86, in which the liposome additionally contains helper lipids.

92. (Previously Presented) The composition according to claim 91, in which said helper lipid is selected from the group consisting of cholesterol, 1-palmitoyl-2-oleoyl phosphatidyl choline or dioleyl phosphatidyl choline.

93. (Previously Presented) The composition according to claim 86, which composition is administered orally, parenterally, intravenously, intramuscularly, subcutaneously, transdermally or in the form of a nasal or mouth spray.

94. (Previously Presented) A method of transporting an antitumor drug to the target organ of a subject in need of antitumor treatment, wherein said drug is selected from the group consisting of taxol or a camptothecin derivative of formula



wherein: R_7 is a $-C(R_{11})=N-O_{(n)}R_{10}$ group, wherein R_{10} is hydrogen or a C_1-C_5 alkyl or C_2-C_5 alkenyl group, linear or branched or C_3-C_{10} cycloalkyl, group or a linear or branched (C_3-C_{10}) cycloalkyl - (C_1-C_5) alkyl group, or C_6-C_{14} aryl, or a linear or branched (C_6-C_{14}) aryl - (C_1-C_5) alkyl group, or a heterocyclic or linear or branched heterocyclo - (C_1-C_5) alkyl group, said heterocyclic group containing at least a heteroatom selected from the group consisting of

nitrogen atom, optionally substituted with a (C_1-C_5) alkyl group, and/or oxygen and/or sulfur; said alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aryl-alkyl, heterocyclic or heterocyclo-alkyl groups, being optionally substituted with other groups selected from the group consisting of: halogen, hydroxy, C_1-C_5 alkyl, C_1-C_5 alkoxy, phenyl, cyano, nitro, -$NR_{12}R_{13}$, wherein R_{12} and R_{13}, which may be the same or different, are hydrogen, linear or branched (C_1-C_5) alkyl; a pharmaceutically acceptable ester of the –COOH group; or the–$CONR_{14}R_{15}$ group, wherein R_{14} and R_{15}, which may be the same or different, are hydrogen or linear or branched (C_1-C_5) alkyl; or

R_{10} is a (C_6-C_{10}) aroyl residue optionally substituted by one or more groups selected from the group consisting of: halogen, hydroxy, linear or branched (C_1-C_5) alkyl, C_1-C_5 alkoxy, phenyl, cyano, nitro, -$NR_{16}R_{17}$, wherein R_{16} and R_{17}, which may be the same or different, are hydrogen, linear or branched (C_1-C_8) alkyl;

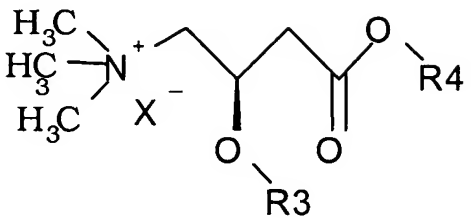
n is the number 0 or 1;

R_{11} is hydrogen, linear or branched C_1-C_5 alkyl, linear or branched C_2-C_5 alkenyl, C_3-C_{10} cycloalkyl, (C_3-C_{10}) cycloalkyl - linear or branched (C_1-C_5) alkyl, C_6-C_{14} aryl, (C_6-C_{14}) aryl - linear or branched alkyl (C_1-C_5);

R_8 and R_9, which may be the same or different are hydrogen, hydroxy, linear or branched C_1-C_5 alkoxy;

their N_1-oxides, their single isomers, in particular the syn and anti isomers of the–$C(R_{11})$=N-$O_{(n)}R_{10}$ group, their possible enantiomers, diastereoisomers and relative admixtures, the pharmaceutically acceptable salts thereof;

said method comprising encapsulating said antitumor drug into a liposome comprising a compound of formula (II)



(II)

where:

R_3 is a saturated linear or branched acyl chain, with 4-26 carbon atoms;

R_4 is a saturated or unsaturated, linear or branched alkyl chain, with 4-26 carbon atoms; and

X^- is the anion of a pharmacologically acceptable acid, to obtain a liposome containing said antitumor drug, and

administering said liposome to said subject.

95. (Previously Presented) The method according to claim 94, in which R_3 is selected from the group consisting of nonanoyl, dodecanoyl, myristoyl, palmitoyl, stearoyl and oleolyl.

96. (Previously Presented) The method according to claim 94, in which R_4 is selected from the group consisting of nonyl, undecyl, tetradecyl, hexadecyl and oleyl.

97. (Previously Presented) The method according to claim 94, in which X^- is selected from the group consisting of chloride; bromide; iodide; aspartate; acid aspartate; citrate; acid citrate; tartrate; acid tartrate; phosphate; acid phosphate; fumarate; acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate; acid maleate; mucate; orotate; oxalate; acid oxalate; sulphate; acid sulphate; trichloroacetate; trifluoroacetate; methane sulphonate; pamoate and acid pamoate.

98. (Previously Presented) The method according to claim 94, in which the compound of formula (II) is selected from the group consisting of palmitoyl L-carnitine chloride undecyl ester; stearoyl L-carnitine chloride undecyl ester; stearoyl L-carnitine chloride tetradecyl ester; palmitoyl L-carnitine chloride tetradecyl ester; myristoyl L-carnitine chloride tetradecyl ester; palmitoyl L-carnitine bromide hexadecyl ester, and oleolyl L-carnitine chloride oleyl ester.

99. (Previously Presented) The method according to claim 94, in which said derivative of camptothecin is selected from the group consisting of 7-benzyloxyiminomethylcamptothecin or 7-butoxyiminomethylcam-ptothecin.

100. (Previously Presented) The method according to claim 94, in which the liposome additionally contains helper lipids.

101. (Previously Presented) The method according to claim 100, in which said helper lipid is selected from the group consisting of cholesterol, 1-palmitoyl-2-oleoyl phosphatidyl choline or dioleyl phosphatidyl choline.

102. (Previously Presented) The method according to claim 94, wherein said antitumor drug is 7-butoxyiminomethylcamptothecin and said liposome comprises the compound palmitoyl L-carnitine undecyl ester.

103. (Previously Presented) The method according to claim 94, wherein said antitumor drug is taxol and said liposome comprises the compound palmitoyl L-carnitine undecyl ester.

104. (Previously Presented) The method according to claim 94, wherein said liposome is administered orally, parenterally, intravenously, intramuscularly, subcutaneously, transdermally or in the form of a nasal or mouth spray.

105. (Previously Presented) The method according to claim 94, wherein lungs are said target organ.

106. (Canceled).

under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn*, 78 USPQ2d at 1335; *see KSR*, 82 USPQ2d at 1396. A claim which is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1396. Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. *See In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

a) Wang et al in combination with Allen, Burke, in further combination with Stracher.

Wang et al.

Wang et al. refer to liposomes prepared from carnitine derivatives, which efficiently complex with DNA and transfer the DNA complex into cells and in mice (page 2201 2nd column).

In particular, liposomes interact with DNA resulting in a change in the membrane properties of the liposome and compaction of DNA, leading to the formation of a tightly packed DNA – lipid complex which must assemble and disassemble during the transfection process. This complex is influenced by the transition temperature of the lipids, which plays an important role during the introduction of DNA into cells, after the complex is internalized (*see* page 2208 column. 1- 2, page 2212 column 1).

Wang et al. disclose the compounds defined as 4a, 4b, 4c, 4d, 4e and 4f (scheme 1 page 2208), chosen for gene delivery.

Wang et al teach that the compounds 4a-f alone have good transfection efficiency only when an helper lipid is present (emphasis added) in the formulation, and the in vitro transfection activity of the alkyl acyl carnitine esters follows the order of 4d > 4e > 4b > 4f > 4c > 4a (page 2211 2nd column). It will be noted that the most efficient liposome of Wang has both C14 alkyl/acyl chains. In the order of efficiency, the following rank is given by Wang et al. (alkyl/acyl chain) C14 > C12 > C18/C18(9) > C16 > C18.

Wang et al. address their study only to liposomes that can be filled in with DNA in order to efficiently transfect in into cells and are completely silent on drug delivery. The liposomes of Wang et al. have the characteristic (transition temperature of lipids) that are needed for forming stable complexes with DNA which are capable to assembly and disassembly during transfection.

According to the present invention, the liposome is efficient in delivering taxol or camptothecin to lung tumor with no need of a helper lipid and the efficiency is not linked to chain length. In the working example, page 55 and following of the specification, the liposome has no helper lipids and the alkyl/acyl chain is C11/C16. It will be noted that C11 alkyl is not provided by Wang et al., and C16 acyl ranks very low in Wang efficiency test.

US6056973 (Allen et al.)

Allen et al. disclose a therapeutic liposome composition comprising:

1. a pre-formed liposome entrapping a therapeutic agent

2. A conjugate composed of:

(a) lipid with a polar head and a hydrophobic tail,

(b) hydrophilic polymer attached to the head of the lipid, and

(c) targeting ligand.

The targeting ligand can be an antibody, a ligand of a receptor, folic acid etc. (column 2, lines 10-57).

Examples of targeting ligand are listed by of Allen et al. in table 1, each of them is specific for a cell type.

The pre-formed liposomes entrap cytotoxic drugs including:

(7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin,

7 -(2-(N-isopropylamino)ethyl) - (20S) - camptothecin,

9-aminocamptothecin and 9-nitrocamptothecin (column 3 lines 1-6).

Allen et al. specifically disclose a E-selectin Fab liposomes which target the endothelial cells along the blood vessels (column 14 lines 63-67, fig 5B), and a liposome with a targeting conjugate which bind to breast cancer (column 16). In vivo results are shown in example 2c (from column 19 line 57 to column 20 line 13).

Allen et al. do not include liposomes comprising a compound of formula (II).

Camptothecins disclosed by Allen et al are not included in camptothecin of formula (IV).

Allen et al. suggest that site targeting can be obtained by adding an additional item to the liposomes which is a targeting ligand. Thus the targeting capability is due to the targeting ligand instead of the liposome itself.

US5552156 (Burke)

Burke et al. disclose liposomes made of lipids (listed in column 6 lines 16-34) including camptothecin as shown in the formulas of column 5. Burke et al. are silent on liposomes comprising a compound of formula (II) and on camptothecin of formula (IV).

The camptothecin-containing liposomes of Burke et al are said to overcome both the insolubility problems and instability problems of the camptothecin drugs administered in their free form, since the lactone ring of the camptothecin drugs is stabilized in the membranes of vesicles (column 2 lines 2-7).

Burke et al. are silent on drug delivery and organ targeting.

US5008288 (Stracher)

Stracher et al. disclose carnitines as carriers (see abstract), which can be incorporated into liposomes (from column 14 to column 17) useful for diminishing the damage incurred during cardiac ischemia resulting from the activation of calcium activated proteases (column lines 45-56). Stracher et al. are silent on tumor.

The present invention claims liposomes comprising compounds of formula (II) which include camptothecins of formula IV, or taxol, and a method for intracellular delivery and organ targeting thereof.

The experimental data, reported in the specification (from page 55 to page 58 and from page 62 to page 63), show that the claimed camptothecin or taxol-containing liposomes have tumor tropism, in particular toward cancer cells in the lung. The experiments demonstrate that the combination of liposomes of formula (II) and camptothecin, or taxol, are more effective than the non-encapsulated active agent in reducing lung metastasis.

The prior art is silent on liposomes including Taxol and does not disclose the camptothecin of formula IV (pages 26-27 of the specification).

In the present invention, the tumor tropism, i.e. the capability of the active agent of moving towards the tumor site, is achieved by the claimed combination, which was specifically designed for this purpose.

The prior art does not suggest that the claimed combination can be used for drug delivery toward specific sites as tumors. In fact, Allen et al. teach that targeting capability is obtained by adding a targeting ligand (for example an antibody) to a liposome. Stracher suggests liposome

delivery in cardiac ischemia, but not in tumors; the other cited documents are silent on this matter.

Thus, neither Allen nor Stracher add features to Wang et al. that lead to the solution proposed in the present application by moving from gene delivery to tumor targeting.

Overlapping of the teachings of Wang with *Allen, Burke, in further combination with Stracher* does not unambiguously give the embodiments of claims 71-78 and 86-105 because they do not give any suggestion on the combination of liposomes of formula (II) and taxol or camptothecins of formula (IV) other then gene delivery (Wang et al.). The combination of the prior art does not give a clear indication that the claimed combination can be efficiently used for targeting drug toward a tumor site (as demonstrate for lung tumor cells).

Hsu US5653996 in combination with Wang

US5653996 (Hsu)

Hsu discloses methods of making liposomes by preparing a first solution of bilayer-forming materials (such as lipids, surfactants, or lipid-like bilayer-forming materials), and a spraying the first solution onto or below the surface of a second solution, thereby forming a liposome suspension. As the solvent is extracted and diluted in the second solution, the bilayer-forming materials become insoluble, forming liposomes instantly (column 4 lines 8-18). Suitable liposome forming materials are listed in column 5.

Hsu is silent on liposomes made of compounds of formula (II). Hsu generally discloses that liposomes can be filled, for example, also with anti-cancer and cytotoxic drugs that can be targeted to a site within the patients.

Wang et al.

Wang et al. is as previously discussed and adds to the general disclosure of Hsu the teaching that liposomes prepared from carnitine derivatives complex with DNA and transfer the DNA complex into cells and in mice. Thus Wang et al. give more information on the use of liposome for gene delivery but do not give any indication on their efficacy in tumor targeting.

This combination does not lead the person with ordinary skills to the solution provided by the present invention. Thus, Hsu does not add skills to the teachings of Wang that can lead the person with the ordinary skills to the embodiments of claims 86-105.

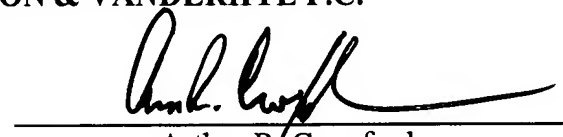
In view of the above claims 86-105 are inventive over Hsu in combination with Wang et al.

Withdrawal of the Section 103 rejection is requested because the claimed invention would not have been obvious to the ordinarily skilled artisan at the time Applicants made their invention.

Having responded to all of the pending rejections contained in the Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

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